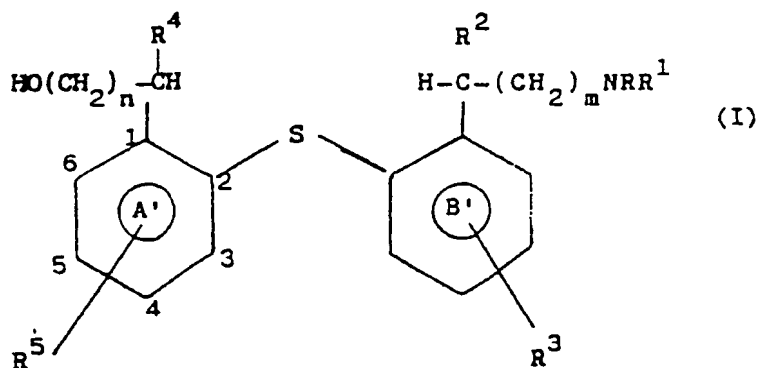




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(54) Title: SUBSTITUTED DIPHENYLSULFIDES AS SEROTONIN UPTAKE INHIBITORS



(57) Abstract

A class of halogen-substituted diphenylsulfide compounds are disclosed. In formula (I), n and m are the same or different and are each 0, 1, 2 or 3; R and R^1 are the same or different and are each hydrogen or straight or branched C_{1-6} alkyl; R^2 and R^4 are the same or different and are each hydrogen or C_{1-4} alkyl; R^3 and R^5 are the same or different and are each hydrogen, halo (e.g. fluoro, bromo, iodo, chloro), trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkylthio, nitro or NR^6R^7 wherein R^6 and R^7 are the same or different and are hydrogen or C_{1-3} alkyl; provided that both R^3 and R^5 are not hydrogen and further provided that when n and m are 0, R^2 and R^4 are hydrogen and R^5 is halo and is in the 5 position of the phenyl ring (A'), then R^3 cannot be hydrogen; or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof, which produce a large selective inhibition of serotonin uptake in brain. Such compounds are useful in the treatment or prevention of a range of depressive conditions as well as anxiety, obsessive compulsive disorders and alcoholism.

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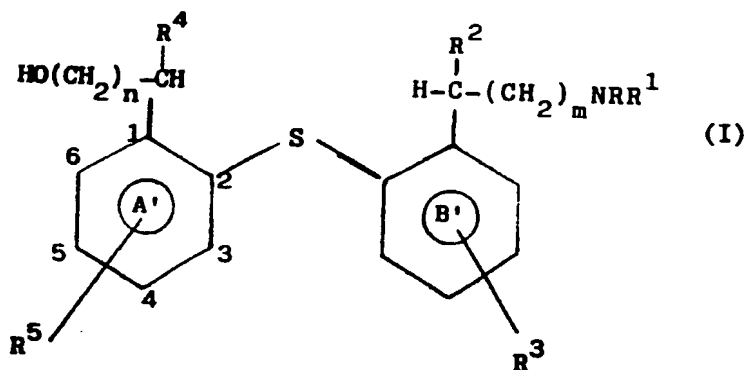
Substituted diphenylsulfides as serotonin uptake inhibitors

The present invention relates to substituted diphenylsulfides, processes for their preparation, pharmaceutical formulations containing them, and their use in medicine, in particular, for the treatment of depression.

Certain 2-hydroxymethyl diphenylsulfides with antidepressant activity are disclosed in U.K. Patent Specification 1,561,072 (U.S. Patent 4,056,632). Compounds which inhibit serotonin uptake are described in U.S. Patent 4,194,009. The use of serotonin uptake inhibitors for treatment of depression is discussed by Benfield *et al.*, *Drugs*, **32**, 481 (1986) and Burrows *et al.*, *J. Clin. Psychiatry*, **49** Suppl. 18 (1988) and in European Patent Application 402097.

The compounds of the present invention selectively inhibit serotonin uptake in brain to a degree which is surprisingly better than the compounds disclosed in U. K. Patent Specification 1,561,072. The compounds of the present invention are therefore useful in the treatment of depression in mammals.

In particular, the present invention is directed to compounds represented by formula (I)



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wherein n and m are the same or different and are each 0, 1, 2 or 3;

R and R¹ are the same or different and are each hydrogen or straight or branched C₁₋₆ alkyl;

R² and R⁴ are the same or different and are each hydrogen or C₁₋₄ alkyl;

R³ and R⁵ are the same or different and are each hydrogen, halo (e.g. fluoro, bromo, iodo, chloro), trifluoromethyl, C₁₋₄ alkyl, C₁₋₄ alkylthio, nitro or NR⁶R⁷ wherein R⁶ and R⁷ are the same or different and are hydrogen or C₁₋₃ alkyl;

provided that both R³ and R⁵ are not hydrogen and further provided that when n and m are 0, R² and R⁴ are hydrogen and R⁵ is halo and is in the 5 position of the phenyl ring (A'), then R³ cannot be hydrogen;

or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof.

Preferably m and n are 0 or 1; R and R¹ are the same or different C₁₋₄ alkyl; R³ and R⁵ are the same or different and are each hydrogen, halo, trifluoromethyl, C₁₋₄ alkoxy or C₁₋₄ alkylthio; and R² and R⁴ are hydrogen or methyl; provided that both R³ and R⁵ are not hydrogen and further provided that when n and m are 0, R² and R⁴ are hydrogen and R⁵ is halo and is in the 5 position of the phenyl ring (A'), then R³ cannot be hydrogen.

Most preferably, m and n are 0; R and R¹ are methyl; R² and R⁴ are hydrogen; R³ and R⁵ are the same or different and are each hydrogen, halo, trifluoromethyl, C₁₋₄ alkoxy or C₁₋₄ alkylthio; provided that both R³ and R⁵ are not hydrogen and further provided that when n and m are 0, R² and R⁴ are hydrogen and R⁵ is halo and is in the 5 position of the phenyl ring (A), then R³ cannot be hydrogen.

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Compounds

2-((2-((Dimethylamino)methyl)phenyl)thio)-5-(trifluoromethyl)benzyl Alcohol and 2-((4-chloro-2-((dimethylamino)methyl)phenyl)thio)-5-trifluoromethyl) benzyl alcohol are especially preferred because of their unusually high specificity for inhibition of serotonin uptake.

Pharmaceutically acceptable esters of formula (I) include carboxylic acid esters in which the non-carbonyl moiety of the ester grouping is selected from straight or branched chain alkyl (e.g., methyl, n-propyl, t-butyl), alkoxyalkyl (e.g., methoxymethyl), aralkyl (e.g., benzyl), aryloxyalkyl (e.g., phenoxymethyl), aryl (e.g., phenyl) optionally substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy, nitro or amino; sulfonate esters such as alkylsulfonyl; or alkylarylsulfonyl (e.g., methanesulfonyl or tolylsulfonyl); and amino acid esters such as the aliphatic and aromatic amino acid esters (e.g., Gly, Ala, Val, Leu, Ile, Phe, Tyr and Trp) and other naturally occurring amino acid esters as well as the ester of L-alanine. Pharmaceutically acceptable acid addition salts of the esters are within the scope of this invention and, where the ester moiety itself contains an amino group, diacid addition salts. In the above ester groups, the alkyl groups (including those in alkoxy groupings) contain 1 to 12 carbon atoms, preferably 1 to 4 carbons, and the aryl groups are preferably phenyl or naphthyl.

Pharmaceutically acceptable acid addition salts of the compounds of formula (I) include those which may be used in intermediate process operations as well as those which are acceptable as final pharmaceutical products. Examples of pharmaceutically acceptable salts of formula (I) are those prepared from e.g., acetic, hydrochloric, sulfuric, phosphoric, toluenesulfonic, maleic, fumaric, tartaric, citric, pamoic, succinic, and nitric acids.

The compounds of formula (I) are serotonin uptake inhibitors as demonstrated by their ability to block the uptake of biogenic amines in rat synaptosomal preparations. The compounds of formula (I) and

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pharmaceutically acceptable salts, esters or other physiologically functional derivative thereof are useful in the treatment of depression in mammals, including humans.

As used herein, the term "physiologically functional derivative" means any physiologically acceptable salt, ester, or salt or such ester, of a compound of formula (I) or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) such a compound or an active metabolite or residue thereof.

The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt ester or other physiologically functional derivative thereof for use in medicine. There is further provided the use of a compound of formula (I) or a pharmaceutically acceptable salt, ester or other physiologically functional derivative thereof in the manufacture of a medicament for treating depression. Additionally, there is provided a method of treating depression in humans which comprises administering to a patient an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, ester or other physiologically functional derivative thereof.

Preferred compounds of formula (I) are:

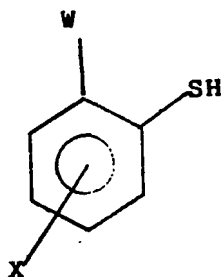
2-((4-chloro-2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol
2-((4-chloro-2-((dimethylamino)methyl)phenyl)thio)-5-(trifluoromethyl)benzyl alcohol
2-((2-((dimethylamino)methyl)phenyl)thio)-5-(trifluoromethyl)benzyl alcohol
4-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol
3-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol
2-chloro-6-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol
5-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)- α -methylbenzyl alcohol

The compounds of formula (I) may be synthesised by any method known in the art for making compounds of an analogous structure.

The compounds of formula (I) may, for example, be prepared as indicated in the following reaction schemes (wherein R , R^1 , R^2 , R^3 , R^4 and R^5 are as hereinbefore defined and p is 1 or 2).

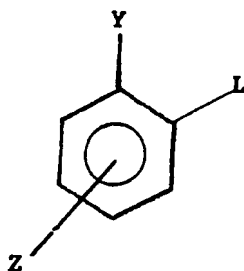
For the purposes of these reaction schemes groups $HO(CH_2)_nCH(R^4)$ and $R^1RN(CH_2)_mCH(R^2)$ in the compounds of formula (I) are referred to as A and B respectively for brevity.

The compounds of formula (I) and precursors thereto may be prepared by reacting a compound of formula (II)



(II)

wherein X is R^3 or R^5 and W is A as hereinbefore defined or a precursor thereto or B as hereinbefore defined or a precursor thereto with a compound of formula (III)



(III)

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wherein Z is R^5 or R^3 , Y is B as hereinbefore defined or a precursor thereto or A as hereinbefore defined or a precursor thereto and L is a suitable leaving group, for example halogen, particularly chlorine.

Compounds of formula (I) having the desired values of A and B may be obtained from the corresponding compounds of formula (I) wherein W and Y are suitable precursors.

Thus, compounds of formula (I) wherein A or B is $\begin{array}{c} R^4 \\ | \\ \text{---} \text{C} \text{---} \text{OH} \\ | \end{array}$ where R^4 is

as hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is -CHO by treatment with $R_4\text{MgBr}$ (Grignard reagent).

Compounds of formula (I) wherein W or Y is -CHO may be obtained from the corresponding compound of formula (I) wherein W or Y is CH_2OH via oxidation, for example with sulfur trioxide-pyridine complex using triethylamine in dimethylsulfoxide.

Compounds of formula (I) wherein W or Y is CH_2OH may be obtained from the corresponding compound of formula (I) wherein W or Y is CO_2Et by reduction with, for example, LAH or directly during the preparation of compounds of formula (I) using the appropriately substituted compounds of formula II or III.

Compounds of formula (I) wherein W or Y is CO_2Et may be obtained by esterification, for example with, ethanol and sulfuric acid of the corresponding compound of formula (I) wherein W or Y is CO_2H .

Compounds of formula (I) wherein W or Y is $\begin{array}{c} R_4 \\ | \\ \text{---} \text{C} \text{---} \text{OH} \\ | \end{array}$ may be obtained

from the corresponding compound of formula (I) wherein W or Y is CHO by a Grignard reaction in THF or ether.

Similarly, compounds of formula (I) wherein A or B is $\text{CH}_2\text{CH}_2(\text{CH}_2)_{p-1}\text{CH}_2\text{OH}$ wherein p is as hereinbefore defined, may be obtained from the corresponding compound of formula (I) wherein W or Y is $\text{CH}=\text{CH}(\text{CH}_2)_{p-1}\text{CO}_2\text{H}$ by reduction with palladium or carbon followed by a hydride reducing agent such as diborane.

Compounds of formula (I) wherein W or Y is $\text{CH}=\text{CH}(\text{CH}_2)_{p-1}\text{CO}_2\text{H}$ may be obtained from the corresponding compound of formula (I) wherein W or Y is CHO by a Knoevenagel-type reaction with a dicarboxylic acid such as malonic acid with an organic base such as piperidine or pyridine or directly during the preparation of compounds of formula (I) using the appropriately substituted compounds of formula (II) or (III). Similarly compounds of formula (I) wherein A or B is

$\begin{array}{c} \text{R}^4 \\ | \\ \text{HC}-\text{CH}_2(\text{CH}_2)_{p-1}\text{CH}_2\text{OH} \end{array}$ wherein R^4 is as hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is $\begin{array}{c} \text{R}^4 \\ \diagdown \\ \text{CH}(\text{CH}_2)_{p-1}\text{CO}_2\text{Et} \end{array}$ wherein R^4 is as hereinbefore defined by

reduction with palladium on carbon following by a hydride reducing agent such as diborane in THF.

Compounds of formula (I) wherein W or Y is $\begin{array}{c} \text{R}^4 \\ \diagdown \\ \text{CH}(\text{CH}_2)_{p-1}\text{CO}_2\text{Et} \end{array}$

wherein R^4 is as hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is $\begin{array}{c} \text{R}^4 \\ \diagdown \\ \text{C}=\text{O} \end{array}$ wherein R^4 is as hereinbefore defined by means of a Wittig reaction.

Compounds of formula (I) wherein W or Y is $\begin{array}{c} \text{R}^4 \\ \diagdown \\ \text{C}=\text{O} \end{array}$ wherein R^4 is as hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is $\begin{array}{c} \text{R}^4 \\ \diagdown \\ \text{C}-\text{OH} \end{array}$ wherein R^4 is as

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hereinbefore defined by oxidation with pyridine chlorochromate (PCC) in methylene chloride.

Compounds of formula (I) wherein W or Y is $\text{R}^4\text{CH}_2\text{OH}$ wherein R^4 is as hereinbefore defined may be prepared from compounds of formula (I) wherein W or Y is CHO by a Grignard reaction in THF or ether.


Similarly, compounds of formula (I) wherein A or B is $\text{R}^2\text{CH}_2(\text{CH}_2)_{p-1}\text{CH}_2\text{NRR}^1$ wherein R, R^1 and R^2 are as hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is $\text{R}^2\text{CH}(\text{CH}_2)_{p-1}\text{CO}_2\text{Et}$ wherein R^2 is as hereinbefore defined by conversion of the ester to an amide group and then reducing the amide to amine, using standard procedures.

Compounds of formula (I) wherein W or Y is $\text{R}^2\text{CH}(\text{CH}_2)_{p-1}\text{CO}_2\text{Et}$ wherein R^2 is as hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is $\text{R}^2\text{CH}(\text{CH}_2)_p\text{CO}_2\text{Et}$ wherein R^2 is as hereinbefore defined by hydrogenation with B_2H_6 .


Compounds of formula (I) wherein W or Y is $\text{R}^2\text{CH}(\text{CH}_2)_{p-1}\text{CO}_2\text{Et}$ wherein R^2 is as hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is $\text{R}^2\text{C}(=\text{O})\text{CH}_2\text{CO}_2\text{Et}$ wherein R^2 is as hereinbefore defined by treatment with $\text{Ph}_3\text{P}(\text{CH}_2)_p\text{CO}_2\text{Et}$.

Compounds of formula (I) wherein W or Y is $\text{R}^2\text{C}(=\text{O})\text{CH}_2\text{CO}_2\text{Et}$ wherein R^2 is as

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hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is R^2  OH wherein R^2 is as

hereinbefore defined by treatment with PCC.

Compounds of formula (I) wherein W or Y is R^2  OH may be obtained

from the corresponding compound of formula (I) wherein W or Y is CH=O by treatment with R^2 MgBr.

Compounds of formula (I) wherein R^2 is CH=O may be obtained from the corresponding compound of formula (I) wherein W or Y is OH by oxidation.

Similarly, compounds of formula (I) wherein A or B is CH_2CH_2OH may be obtained from the corresponding compound of formula (I) wherein W or Y is CHO or directly during the preparation of compounds of formula (I) using the appropriate substituted compounds of formula (II) or (III) by Horner-Wadsworth-Emmons Chemistry as described in Agnew, Chem., 80, 364 (1968) followed by reduction with a hydride reducing agent such as diborane.

Similarly, compounds of formula (I) wherein A or B is CH_2OH may be obtained from the corresponding compound of formula (I) wherein W or Y is CHO by reduction, for example with diborane in tetrahydrofuran (THF).

Similarly, compounds of formula (I) wherein A or B is $CH_2CH_2(CH_2)_{p-1}CH_2NRR^1$ wherein R and R^1 are as hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is $CH=CH(CH_2)_{p-1}CONRR^1$ wherein p, R and R^1 are as hereinbefore defined by reduction with palladium or carbon followed by a hydride reducing agent such as diborane.

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Compounds of formula (I) wherein W or Y is $\text{CH}=\text{CH}(\text{CH}_2)_{p-1}\text{CONRR}^1$ wherein p, R and R^1 are as hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is $\text{CH}=\text{CH}(\text{CH}_2)_{p-1}\text{CO}_2\text{H}$ wherein p is as hereinbefore defined by reaction with thionyl chloride followed by the appropriate amine.

Compounds of formula (I) wherein W or Y is $\text{CH}=\text{CH}(\text{CH}_2)_{p-1}\text{CO}_2\text{H}$ wherein p is as hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is CHO by homologation in a Knoevenagel-type reaction, for example, with a dicarboxylic acid, such as malonic acid, with an organic base, such as piperidine or pyridine at a temperature from 80°C to 150°C.

Similarly, compounds of formula (I) wherein A or B is $\text{CH}_2\text{CH}_2\text{NRR}^1$ wherein R and R^1 are as hereinbefore defined may be obtained from the corresponding compound of formula (I) wherein W or Y is $\text{CH}_2\text{CH}_2\text{NH}_2$ by standard alkylation reactions.

Compounds of formula (I) wherein W or Y is $\text{CH}_2\text{CH}_2\text{NH}_2$ may be obtained from the corresponding compound of formula (I) wherein W or Y is $\text{CH}=\text{CHNO}_2$ by reduction, for example with LAH.

Compounds of formula (I) wherein W or Y is $\text{CH}=\text{CHNO}_2$ may be obtained from the corresponding compound of formula (I) wherein W or Y is CHO by reaction with nitromethane in a mild base such as ammonium acetate in acetic acid.

Compounds of formula (I) wherein W or Y is CO_2H may be prepared from the corresponding compound of formula (I) wherein W or Y is CONRR^1 wherein R and R^1 are as hereinbefore defined by basic hydrolysis.

Compounds of formula (I) wherein A or B is CH_2NRR^1 wherein R and R^1 are as hereinbefore defined may be prepared from the corresponding compound of formula (I) wherein W or Y is CONRR^1 wherein R and R^1 are


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as hereinbefore defined by reduction, for example with diborane in tetrahydrofuran (THF).


Compounds of formula (I) wherein A or B is CH_2NRR^1 wherein R and R^1 are as hereinbefore defined may be prepared from the corresponding compound of formula (I) wherein W or Y is CONRR^1 wherein R and R^1 are as hereinbefore defined by reduction with a reducing agent such as lithium aluminium hydride (LAH).

Similarly, compounds of formula (I) wherein A or B is CH_2NRR^1 wherein R and R^1 are as hereinbefore defined may be prepared from the corresponding compound of formula (I) wherein W or Y is CH_2NH_2 by alkylation using standard methods of organic chemistry. Compounds of formula (I) wherein W or Y is CH_2NH_2 may be prepared from the corresponding compound of formula (I) wherein W or Y is CN by reduction, for example with diborane in THF.

Similarly, compounds of formula (I) wherein A or B is $\text{HOH}_2\text{C}(\text{CH}_2)_{p-1}\text{H}_2\text{C}-\text{R}^4$ wherein R^4 is as hereinbefore defined may be

prepared from the corresponding compound of formula (I) wherein W or Y is  by a series of reactions: deprotection of the aldehyde group

with, for example, hydrochloric acid; Grignard reaction; oxidation, for example with pyridine chlorochromate; a Wittig reaction; and reduction, for example with a metal catalyst followed by a hydride reducing agent such as borane.

Compounds of formula (I) wherein W or Y is  may be prepared from

the corresponding compound of formula (I) wherein W or Y is CHO by treatment with $\text{HOCH}_2\text{CH}_2\text{OH}$.

Compounds of formula (I) wherein W or Y is CHO may be prepared from the corresponding compound of formula (I) wherein W or Y is CO_2Et firstly by reduction at 0°C with a hydride reducing agent such as LAH and then by oxidation, for example, with sulfur trioxide-pyridine complex in triethylamine and dimethylsulfoxide.

Compounds of formula (I) wherein W or Y is $\text{CH}_2\text{CH}_2\text{OH}$ may be prepared from the corresponding compound of formula (I) wherein W or Y is CH_2COOH by reduction, for example with diborane.

Compounds of formula (I) wherein W or Y is CH_2COOH may be prepared from the corresponding compound of formula (I) wherein W or Y is CHO by a Horner-Wadsworth-Emmons reaction as hereinbefore described.

Compounds of formula (I) wherein W or Y is CH_2OH may be prepared from the corresponding compound of formula (I) wherein W or Y is CO_2H by reduction, for example, with diborane in THF.

Compounds of formula (I) wherein A or B is CH_2NMe_2 may be prepared from the corresponding compound of formula (I) wherein W or Y is CONMe_2 by reduction with, for example LAH.

Compounds of formula (I) wherein A or B is $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ may be prepared from the corresponding compound of formula (I) wherein W or Y is $\text{EtO}_2\text{C}-\text{CH}=\text{CH}$ by reduction with, for examples LAH (two equivalents).

Compounds of formula (I) wherein W or Y is $\text{EtO}_2\text{C}-\text{CH}=\text{CH}$ may be prepared from the corresponding compound of formula (I) wherein W or Y is CHO by treatment with triethylphosphonoacetate and THF.

Compounds of formula (I) wherein W or Y is $\text{CH}_2-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{NH}$ may be

prepared from the corresponding compound of formula (I) wherein W or Y is $\text{CH}_2-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \end{array} \text{N}-\text{CO}_2\text{Et}$ by base hydrolysis using for example ethanolic KOH.

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Compounds of formula (I) wherein A or B is CH_2NHCH_3 may be prepared from the corresponding compound of formula (I) wherein W or Y is CH=NCH_3 by reduction with NaBH_4 .

Compounds of formula (I) wherein W or Y is CH=NCH_3 may be prepared from the corresponding compound of formula (I) wherein W or Y is CHO by treatment with MeNH_2 in the presence of an acid such as PTSA.

Compounds of formula (I) wherein A or B is CH_2OH may be formed directly by the reaction of compounds (II) and (III) wherein (II) or (III) is appropriately substituted.

Compounds of formula (I) wherein A or B is CH_2NMe_2 may be prepared from the corresponding compound of formula (I) wherein W or Y is CHO by reductive amination using for example NaCNBH_3 and Me_2NH .

Compounds of formula (I) wherein A or B is $\text{CH}_2\text{CH}_2\text{CH}_2\text{NMe}_2$ may be prepared from the corresponding compound of formula (I) wherein W or Y is $\text{CH=CHCH}_2\text{NMe}_2$ by hydrogenation in the presence of a metal catalyst, for example, Palladium, in the presence of AcOH .

Compounds of formula (I) wherein W or Y is $\text{CH=CHCH}_2\text{NMe}_2$ may be prepared from the corresponding compound of formula (I) wherein W or Y is CHO by treatment with $\text{Me}_2\text{NCH}_2\text{CH}_2\text{PPh}_3\text{Br}$, HCONH_2 and K_2CO_3 (Wittig).

Esters of formula (I) may be prepared by methods well known in the art of organic chemistry, for example, treatment of the alcohol with an acid halide in the presence of an appropriate acid acceptor such as triethylamine. Acid addition salts may be prepared by reaction in a suitable solvent with appropriate acid.

The compounds of this invention or pharmaceutically acceptable esters salts, or other physiologically functional derivatives thereof may be administered orally, parenterally transdermally or rectally.

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The compounds of formula (I) and pharmaceutically acceptable esters, salts and other physiologically functional derivatives thereof may be used in treating depression of three main types: neurotic or reactive depression with anxiety, somatic concern and tension; psychotic or endogenous depression with emotional withdrawal, motor retardation, blunted affect, guilt feelings and conceptual disorganization; and a group showing features of both neurotic and psychotic depression with hostility and suspiciousness. Compounds of formula (I) and pharmaceutically acceptable esters, salts and other physiologically functional derivatives thereof may also be used for the treatment of anxiety, obsessive compulsive disorders, and alcoholism. (See *Diagnosis and Statistical Manual of Mental Disorders*, third edition, - revised 1987, for descriptions of the above mentioned disorders.) Compounds of formula (I) and pharmaceutically acceptable esters, salts and other physiologically functional derivatives thereof may also be used to potentiate the analgesic effect of morphine or like opiate analgesics.

The preferred antidepressant dosage for parenteral administration of a compound of formula (I) (calculated as the base) is 0.5 mg/kg to 40 mg/kg of mammal body weight per day, and the most preferred dosage is 1 mg/kg to 10 mg/kg of mammal body weight per day. For the oral and rectal mode of administration, the preferred antidepressant dosage of a compound of formula (I) (calculated as the base) is about 1 mg/kg to 50 mg/kg of mammal body weight per day, while the most preferred dosage (estimated as the base) is 1 mg/kg to 20 mg/kg of mammal body weight per day. A compound of formula (I), or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof, is preferably administered four times daily although the number of daily administrations of the medication and the total dose will vary according to the mammal being treated, and according to the exercise of the physician's discretion.

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For example, for the treatment of depression in humans, the preferred unit dosage of a compound of formula (I) or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof (calculated as the base) for oral administration, or administration as a suppository, is about 5 mg to 300 mg, with the more preferred unit dosage being about 15 mg to 250 mg, and the most preferred unit dosage being about 25 mg to 200 mg. All the above doses are given in term of the weight of a compound of formula (I) in the form of its base, but as will be appreciated from the foregoing information, doses are preferably administered in the form of a pharmaceutically acceptable ester or salt of a compound of formula (I). The preferred dosage for the treatment of anxiety, obsessive compulsive disorders and alcoholism are the same as dosages described above for the treatment of depression. For decreasing the amount of morphine required for analgesia the preferred dosage of compounds of formula (I) and pharmaceutically acceptable esters, salts or other physiologically functional derivative thereof (calculated as the base) are three to four times greater than the dosages required for depression, anxiety or obsessive compulsive disorders.

According to the present invention, in yet another aspect, there is provided a pharmaceutical composition, preferably in unit dosage form, comprising a compound of formula (I), or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof, together with a pharmaceutically acceptable carrier.

A pharmaceutical composition containing a compound of formula (I), or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof, may be presented in discrete units such as tablets, capsules, ampoules (i.e., for injection), suppositories or liposome formulations each containing an effective antidepressant non-toxic amount of the compound and one or more pharmaceutically acceptable carriers.

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Conveniently the compound of formula (I) or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof comprises from 5 to 95% by weight of the composition.

The pharmaceutical compositions may be in the form of an oral unit dose preparation for example a cachet, tablet or capsule. Suitable pharmaceutically acceptable carriers for such compositions include solid diluents such as lactose, cornstarch, micronized silica gel, or merely the capsule shell as well as other excipients well known in the art for this purpose.

The pharmaceutical compositions may further take the form of those suitable for rectal use as a suppository with the usual pharmaceutically acceptable carriers such as cocoa butter. Those for parenteral use include an ampoule of a sterile solution or suspension with water or other pharmaceutically acceptable liquid as the carrier therefor, or an ampoule of a sterile powder for dilution with a pharmaceutically acceptable liquid.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved and/or dispersed in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%. As one particular possibility, the active compound may be delivered from the patch by electrotransport iontophoresis as generally described in *Pharmaceutical Research*, 3(6), 318 (1986).

It should be understood that in addition to the aforementioned ingredients, the pharmaceutical compositions of this invention may include one or more of additional ingredients such as diluents, buffers, flavoring agents, binders, surface active agents, thickeners, lubricants, preservatives, and the like. The compositions may be

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prepared by admixture of the ingredients, and, if necessary, shaping the resulting mass, and filling into suitable containers.

The following examples are provided by way of an illustration of the present invention and should in no way constitute a limitation thereof.

EXAMPLE 1

Preparation of 2-((3-Chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide

Potassium carbonate (4.76 g) was added to a solution of 2,6-dichlorobenzaldehyde and 2-thio-N,N-dimethylbenzamide (Schindlbauer, Monatsch. Chem., 99 (5), 1799 (1968) (6.25 g) in 52 mL of dimethylformamide. The reaction mixture was stirred at 160°C for three hours. Brine was added and product was extracted with EtOAc. Purification by liquid chromatography on silica gel with toluene/EtOAc 1:1 gave 5.56 g (50.4% yield) of 2-((3-chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide as an oil.

Anal. Calcd. for $C_{16}H_{14}ClNO_2S$; C, 60.09; H, 4.41; Cl, 11.09; N, 4.38; S, 10.03.

Found: C, 60.17; H, 4.46; Cl, 11.07; N, 4.34; S, 9.97.

EXAMPLE 2

Preparation of 2-Chloro-6-((2-((dimethylamino)methyl)phenyl)thio)-benzyl Alcohol

2-((3-Chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide (5.5 g) was dissolved in 16 mL of anhydrous tetrahydrofuran and, under nitrogen, 44.7 mL of 1.0 M diborane was added while keeping the reaction mixture cold. The resulting solution was refluxed overnight. The reaction mixture was treated with 46 mL of 6 N HCl and refluxed for three hours. Treatment with 50% NaOH and extraction with $CHCl_3$ gave the

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free base as an oil. To the base in EtOAc was added an excess of EtOAc/HCl. The hydrochloride salt was triturated with acetone to give 3.76 g (63.5% yield) of 2-chloro-6-((2-((dimethylamino)methyl)-phenyl)thio)benzyl alcohol hydrochloride, m. p. 153-154°C.

Anal. Calcd. for $C_{16}H_{18}Cl \cdot NOS \cdot HCl$; C, 55.82; H, 5.56; Cl, 20.59; N, 4.07; S, 9.31.

Found: C, 55.94; H, 5.59; Cl, 20.50; N, 4.00; S, 9.41.

1H NMR (Me_2SO-d_6): δ 2.725 (s, 6H, NMe_2); 4.401 (s, 2H, NCH_2) 4.794 (s, 2H, OCH_2); 5.321 (s, 1H, OH); 6.739-7.892 (m, 7H, aromatic); 10.507 (s, 1H, NH).

EXAMPLE 3

Preparation of 2-((4-Chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide

Potassium carbonate (27.6 g) was added to a solution of 2,5-dichlorobenzaldehyde (30.2 g) (Bondinell *et al.*, J. Med. Chem., **23** (5), 506 (1980)) and 2-thio-N,N-dimethylbenzamide (Schindlbauer, Monatsch. Chem., **99** (5), 1799 (1968)) (36.3 g) in 500 mL of dimethylformamide. The reaction mixture was stirred at 160°C for four hours, added to 2.5 liters of chilled water, and extracted with EtOAc to give 50.2 g of a tan solid. Recrystallization from acetone/hexane mixtures gave 43.5 g (80% yield) of 2-((4-chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide, m.p. 87-88°C.

Anal. Calcd. for $C_{16}H_{14}ClNO_2S$; C, 60.09; H, 4.41; N, 4.38; S, 10.03.
Found: C, 60.16; H, 4.42; N, 4.36; S, 9.97.

EXAMPLE 4

Preparation of 2-((4-Chloro-2-(1-hydroxyethyl)phenyl)thio)-N,N-dimethylbenzamide

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Methylmagnesium bromide, 3.0 M solution in Et_2O (8.1 mL), was added to a suspension of 2-((4-chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide (7.0 g) in anhydrous Et_2O (55 mL) under nitrogen. The reaction mixture was refluxed for two hours. The addition compound was decomposed by treatment with 25% aqueous NH_4OH (5.4 mL). The reaction mixture was filtered and the filtrate was concentrated in vacuo and chromatographed on silica gel with toluene/EtOAc (2:1) to afford 5.79 g (78.7% yield) of 2-((4-chloro-2-(1-hydroxyethyl)phenyl)thio)-N,N-dimethylbenzamide as a yellow oil.

EXAMPLE 5

Preparation of 5-Chloro-2-((2-((dimethylamino)methyl)phenyl)thio)- α -methylbenzyl Alcohol

This compound was prepared from 2-((4-chloro-2-(1-hydroxyethyl)phenyl)thio)-N,N-dimethylbenzamide following the procedure of example 2. The free base was chromatographed on silica gel with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (1:1) to afford a light yellow oil. To the base in EtOAc was added an excess of EtOAc/HCl to give 2.61 g (42.2% yield) of 5-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)- α -ethylbenzyl alcohol hydrochloride as a white solid, m.p. 149-151°C.

Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{Cl}$ NOS·HCl; C, 56.98; H, 5.91; Cl, 19.79; N, 3.91; S, 8.95.

Found: C, 57.09; H, 5.95; Cl, 19.84; N, 3.96; S, 8.87.

$^1\text{H NMR}$ ($\text{Me}_2\text{SO}-d_6$): δ 1.296 (d, 3H, Me); 2.745 (s, 6H, Me_2N); 4.404 (s, 2H, NCH_2); 5.036-5.120 (m, 1H, OCH); 5.543 (d, 1H, OH); 6.931 (d, 1H, aromatic); 7.165-7.492 (m, 4H, aromatic); 7.605 (d, 1H, aromatic); 7.790-7.835 (m, 1H, aromatic); 10.500 (s, 1H, NH).

EXAMPLE 6

Preparation of 2-((5-Chloro-2-formylphenyl)thio)-N,N-dimethyl-

benzamide

This compound was prepared from 2,4-dichlorobenzaldehyde by following the procedure from example 1 to give 8.9 g (80.7% yield) of 2-((5-chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide as an oil.

EXAMPLE 7Preparation of 4-Chloro-2-((2-((dimethylamino)methyl)phenyl)thio)-benzyl Alcohol

This compound was prepared by using 2-((5-chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide and following the procedure from example 2 to give 4.24 g (62% yield) of 4-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol hydrochloride as a white powder, m.p. 158-160°C.

Anal. Calcd. for $C_{16}H_{18}Cl \cdot NOS \cdot HCl$; C, 55.82; H, 5.56; Cl, 20.59; N, 4.07; S, 9.31.

Found: C, 55.72; H, 5.58; Cl, 20.67; N, 4.04; S, 9.24.

1H NMR (Me_2SO-d_6): δ 2.737 (s, 6H, NMe_2); 4.429 (s, 2H, NCH_2); 4.505 (s, 2H, OCH_2); 5.462 (br s, 1H, OH); 7.178-7.867 (m, 7H, aromatic); NH not found.

EXAMPLE 8Preparation of 2-((6-Chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide

This compound was prepared from 2,3-dichlorobenzaldehyde by following the procedure from example 1 to give 8.84 g (80% yield) of 2-((6-chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide as a beige solid, m.p. 119-121°C.

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Anal. Calcd. for $C_{16}H_{14}ClNO_2S$; C, 60.09; H, 4.41; Cl, 11.09; N, 4.38; S, 10.03.

Found: C, 60.19; H, 4.43; Cl, 11.01; N, 4.31; S, 9.97.

EXAMPLE 9

Preparation of 3-Chloro-2-((2-((dimethylamino)methyl)phenyl)thio)-benzyl Alcohol

This compound was prepared from 2-((6-chloro-2-formylphenyl)thio)-N,N-dimethylbenzamide by following the procedure from example 2 to give 6.96 g (73.7% yield) of 3-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol hydrochloride as a white powder, m.p. 180-182°C.

Anal. Calcd. for $C_{16}H_{18}ClNOS \cdot HCl$; C, 55.82; H, 5.56; Cl, 20.59; N, 4.07; S, 9.31.

Found: C, 55.57; H, 5.59; Cl, 20.49; N, 4.05; S, 9.23.

1H NMR (Me_2SO-d_6): δ 2.822 (s, 6H, NMe_2); 4.508 (s, 2H, NCH_2); 4.598 (s, 2H, OCH_2); 5.517 (br s, 1H, OH); 6.537-7.725 (m, 7H, aromatic); NH not found.

EXAMPLE 10

Preparation of 2-Chloro-5-trifluoromethylbenzaldehyde

To a solution of 3-bromo-4-chlorobenzotrifluoride (32 g) in 81 mL of anhydrous tetrahydrofuran at -60°C under nitrogen was added 52 mL of 2.5 M n-BuLi. The resulting solution was stirred for thirty minutes and 19.1 mL of dimethylformamide was added, while keeping the temperature at -60°C. The reaction mixture was stirred for one hour, allowing it to warm to room temperature. Water (23 mL) was added and the dark mixture was allowed to warm to room temperature overnight. Additional water was added (23 mL), the layers were separated, and the

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aqueous phase was extracted with toluene to afford a brown oil. Purification by distillation gave 12.36 g (48% yield) of 2-chloro-5-trifluoromethylbenzaldehyde as a yellow oil, b.p. 92-98°C.

EXAMPLE 11

Preparation of 2-((2-Formyl-4-(trifluoromethyl)phenyl)thio)-N,N-dimethylbenzamide

This compound was prepared by following the procedure from example 1, using 2-chloro-5-trifluoromethylbenzaldehyde, to give 5.11 g (42% yield) of 2-((2-formyl-4-(trifluoromethyl)phenyl)thio)-N,N-dimethylbenzamide as a light yellow solid, m.p. 134-135°C.

Anal. Calcd. for $C_{17}H_{14}F_3NO_2S$; C, 57.78; H, 3.99; N, 3.96; S, 9.07.
Found: C, 57.77; H, 4.01; N, 3.93; S, 9.14.

EXAMPLE 12

Preparation of 2-((2-((Dimethylamino)methyl)phenyl)thio)-5-(trifluoromethyl)benzyl Alcohol

This compound was prepared from 2-((2-formyl-4-(trifluoromethyl)phenyl)thio)-N,N-dimethylbenzamide by following the procedure from example 2 to give 3.13 g (58% yield) of 2-((2-((dimethylamino)methyl)phenyl)thio)-5-(trifluoromethyl)benzyl alcohol hydrochloride as a white powder, m.p. 126-128°C.

Anal. Calcd. for $C_{17}H_{18}F_3NOS \cdot HCl$; C, 54.04; H, 5.07; Cl, 9.38; N, 3.71; S, 8.49.
Found: C, 53.92; H, 5.09; Cl, 9.46; N, 3.67; S, 8.57.

1H NMR (Me_2SO-d_6): δ 2.731 (s, 6H, NMe_2); 4.398 (s, 2H, NCH_2); 4.656 (s, 2, OCH_2); 5.688 (br s, 1H, OH); 6.811 (d, 1H, aromatic); 7.484-7.645

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(m, 4H, aromatic); 7.806 (s, 1H, aromatic); 7.909 (d, 1H, aromatic), NH not found.

EXAMPLE 13

Preparation of 2-Thio-5-chloro-N,N-dimethylbenzamide

This compound was prepared from 2,2'-dithiobis(5,-chlorobenzoic acid) by following the procedure from Schindlbauer (Monatsch. Chem., 99 (5), 1799 (1968)) to give 6.20 g (60% yield) of crude 2-thio-5-chloro-N,N-dimethylbenzamide as a yellow oil.

EXAMPLE 14

Preparation of 5-Chloro-2-((2-formylphenyl)thio)-N,N-dimethylbenzamide

This compound was synthesized from 2-thio-5-chloro-N,N-dimethylbenzamide and 2-chlorobenzaldehyde by following the procedure from example 1 to give 3.17 g (69% yield) of 5-chloro-2-((2-formylphenyl)thio)-N,N-dimethylbenzamide as a yellow oil.

Anal. Calcd. for $C_{16}H_{14}ClNO_2S$; C, 60.09; H, 4.41; Cl, 11.09; N, 4.38; S, 10.03.

Found: C, 60.37; H, 4.49; Cl, 10.92; N, 4.25; S, 9.84.

EXAMPLE 15

Preparation of 2-((4-Chloro-2-((dimethylamino)methyl)phenyl)thio)-benzyl Alcohol

This compound was prepared from 5-chloro-2-((formylphenyl)thio)-N,N-dimethylbenzamide by following the procedure from example 2 to give 2.53 g (74.3%) of 2-((4-chloro-2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol hydrochloride as a white solid, m.p. 188-190°C.

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Anal. Calcd. for $C_{16}H_{18}Cl$ $NOS \cdot HCl$; C, 55.98; H, 5.58; Cl, 20.65; N, 4.08; S, 9.34.

Found: C, 55.90; H, 5.57; Cl, 20.53; N, 4.03; S, 9.41.

1H NMR (Me_2SO-d_6): δ 2.768 (s, 6H, NMe_2); 4.434 (s, 2H, NCH_2); 4.552 (s, 2H, OCH_2); 5.405 (br s, 1H, OH); 7.051-7.597 (m, 6H, aromatic); 7.970 (s, 1H, aromatic); 10.607 (s, 1H, NH).

EXAMPLE 16

Preparation of 5-Chloro-2-((4-trifluoromethyl-2-formylphenyl)thio)-N,N-dimethylbenzamide

This compound was synthesized from 2-thio-5-chloro-N,N-dimethylbenzamide and 2-chloro-5-trifluoromethylbenzaldehyde by following the procedure from example 1 to give 4.64 g (83.5% yield) of 5-chloro-2-((4-trifluoromethyl-2-formylphenyl)thio)-N,N-dimethylbenzamide as a light brown oil.

EXAMPLE 17

Preparation of 2-((4-Chloro-2-((dimethylamino)methyl)phenyl)thio)-5-(trifluoromethyl)-benzyl Alcohol

This compound was prepared from 5-chloro-2-((4-trifluoromethyl-2-formylphenyl)thio)-N,N-dimethylbenzamide by following the procedure from example 2 to give 2.51 g (50.9% yield) of 2-((4-chloro-2-((dimethylamino)methyl)phenyl)thio)-5-(trifluoromethyl)-benzyl alcohol hydrochloride as a white solid, m.p. 201-203°C.

Anal. Calcd. for $C_{17}H_{17}ClF_3NOS \cdot HCl$; C, 49.52; H, 4.40; Cl, 17.20; N, 3.40; S, 7.78.

Found: C, 49.54; H, 4.44; Cl, 17.28; N, 3.44; S, 7.69.

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¹H NMR (Me₂SO-d₆): δ 2.741 (s, 6H, NMe₂); 4.399 (s, 2H, NCH₂); 4.648 (s, 2H, OCH₂); 5.689 (br s, 1H, OH); 6.910 (d, 1H, aromatic); 7.448-7.633 (m, 3H, aromatic); 7.817 (s, 1H); 8.074 (s, 1H, aromatic); 10.548 (s, 1H, NH).

EXAMPLE 18

Preparation of (E)-ethyl 5-chloro-2-((2-(N,N-dimethylcarbamoyl)-phenyl)thio)cinnamate

To a mixture of 0.52g of NaH in 62ml of anhydrous THF under N₂ was added a solution of triethylphosphonoacetate (4.58g) also 62mg of THF, allowed to stir at room temperature until a clear solution was obtained. Subsequently a solution of 2-((4-chloro-2-formylphenyl)-thio)-N,N-dimethylbenzamide (6.92g) in 50ml of THF was added dropwise and the reaction mixture was stirred at room temperature overnight. A small amount of H₂O was added to quench the reaction and the organic, solvent was concentrated in vacuo. The residue was partitioned between H₂O and EtoAc. The organic layer was washed with brine, dried (Na₂SO₄) filtered and evaporated to dryness. Purified by LC on silica gel with hexanes/EtoAc (2:1) to afford 5.56g (66%) of (E)-ethyl 5-chloro-2-((2-(N,N-dimethylcarbamoyl)phenyl)thio)cinnamate as a white solid, mp. 114-116°C.

Anal. Calc. for C₂₀H₂₀ClNO₃S; C, 61.61; H, 5.17, Cl, 9.09; N, 3.59; S, 8.22

Found: C, 61.63; H, 5.21; Cl, 9.01; N, 3.62; S, 8.16

EXAMPLE 19

Preparation of 3-(5-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)-phenyl)propanol

To a suspension of Li Al H₄ (2.11g) also 295ml of anhydrous THF under N₂ was added a solution of (E)-ethyl 5-chloro-2-((2-(N,N-dimethylcar-

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bamoyl)phenyl)thio)cinnamate (6.2g) in 40ml of anhydrous THF. Heated at reflux overnight quenched with dropwise addition of 15% NaOH to pH 10-11. Solvent was evaporated to dryness and the residue was dissolved in 10% HCL and extracted with EtOAc, only non polar materials were present. The aqueous layer was evaporated to dryness and the residue was taken up in MeOH, an insoluble material which precipitated was filtered and the methanolic filtrate was evaporated to dryness. Purified by LC on silica gel with 5% MeOH/CH₂Cl₂. Further purification was carried out on silica gel with 5% MeOH/EtOAc. Desired product was then dissolved in MeOH and treated with Et₂O/HCl to afford 0.104g (2%) of 3-(5-chloro-2-((2-((dimethylamino)-methyl)phenyl)thio)phenyl) propanol hydrochloride as a pale yellow oil.

Anal. Calc. for C₁₈H₂₂Cl NOS.HCl 1.60, H₂O; C, 53.89; H, 6.58; Cl, 17.67; N, 3.49; S, 7.99

Found: C, 53.64; H, 6.54; Cl, 17.48; N, 3.47; S, 7.87

EXAMPLE 20

Preparation of Ethyl 4-(2-((4-chloro-2-formylphenyl)thio)benzoyl)-1-piperazinecarboxylate

Potassium carbonate (4.84g) was added to a solution of 2,5-dichloro-benzaldehyde (6.13g) (Bondinell *et al.*, J.Med.Chem., 23 (5), 506 (1980)) and 2-thio(ethyl-1-piperazinecarboxylate)benzamide (10.32g) (prepared by the method of Schindlbauer, Monatsch. Chem., 99 (5), 1799 (1968)) in 54ml of dimethylformamide. The reaction mixture was stirred at reflux for three hours. It was allowed to cool to room temperature and partitioned between 84ml of brine and 64ml of EtOAc, the aqueous layer was extracted with 3 portions of 165ml of EtOAc. The combined organic layers were washed with four 60ml portions of brine. The organic layers combined gave a dark brown oil which was purified by LC on silica gel with hexanes/EtOAc (1:1) to afford 7.06g

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(47%) of ethyl 4-(2-((4-chloro-2-formylphenylthio)benzoyl)-1-piperazinecarboxylate as a yellow oil.

Anal. Calc. for $C_{21}H_{21}ClN_2O_4S$; C, 58.26; H, 4.89; Cl, 8.19; N, 6.47; S, 7.41

Found: C, 58.16; H, 4.94; Cl, 8.25; N, 6.39; S, 7.47

EXAMPLE 21

Preparation of 5-Chloro-2-((2-(4-ethylcarboxylate-1-piperazinemethyl)phenyl)thio)benzyl alcohol

This compound was prepared from ethyl 4-(2-((4-chloro-2-formylphenyl)thio)benzoyl)-1-piperazinecarboxylate following the procedure of Example 2. The free base was chromatographed on silica gel with hexanes/EtoAc (2:1) to afford 5.66g (84%) of 5-chloro-2-((2-(4-ethylcarboxylate-1-piperazinemethyl)phenyl)thio)benzyl alcohol as a pale yellow oil.

EXAMPLE 22

Preparation of 5-Chloro-2-((2-(1-piperazinemethyl)phenyl)thio)benzyl alcohol

To a solution of KOH (10.76g) in 150ml of 95% EtoH was added 5-chloro-2-((2-(4-ethylcarboxylate-1-piperazinemethyl)phenyl)thio)benzyl alcohol and the reaction mixture was heated at reflux overnight. The pH of the reaction was raised from 14 to 12 with concentrated HCl and ethanol was evaporated. Water was added and the product was extracted with EtoAc and chromatographed on silica gel with CH_2Cl_2 /MeOH/H₂O (5:4:1). The free base was dissolved in MeOH and treated with 1,4-dioxane/HCl, the solid which precipitated was filtered and thoroughly washed with ether to give 5-chloro-2-((2-(1-piperazinemethyl)phenyl)thio)benzyl alcohol hydrochloride as an off-white powder mp. 230-231°C dec.

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Anal. Calc. for $C_{18}H_{21}ClN_2OS \cdot 2HCl \cdot 0.35H_2O$; C, 50.50; H, 5.58; Cl, 24.84; N, 6.54; S, 7.49

Found: C, 50.43; H, 5.56; Cl, 24.54; N, 6.41; S, 7.28

EXAMPLE 23

Preparation of 2,2'-Dithiobis(5-chlorobenzyl alcohol)

This compound was prepared from 2,2'-dithiobis(5-chlorobenzoic acid) by following the procedure from Nung Min Yoon (J.Org.Chem. **38** (16), 2876 (1973)). Purification by ligand chromatography on silica gel with 1% MeOH/ CH_2Cl_2 gave 19.7g (69%) of 2,2'-dithiobis(5-chlorobenzyl alcohol) as a yellow foam.

EXAMPLE 24

Preparation of 2-Mercapto-5-chlorobenzyl alcohol

2,2'-dithiobis(5-chlorobenzyl alcohol) (19.6g) and 300ml of ethanol was stirred at room temperature until a solution was obtained. Sodium borohydride (7.63g) was added in several portions and the reaction mixture was refluxed for 2hrs. Concentrated hydrochloric acid was added to pH 2. Ethanol was evaporated and water was added (200ml). Product was extracted with ethyl acetate to give 19.3g (98%) of 2-mercapto-5-chlorobenzyl alcohol as a yellow solid.

EXAMPLE 25

Preparation of 2-((4-Chloro-2-(hydroxymethyl)phenyl)thio)-5-(trifluoromethyl)benzaldehyde

This compound was prepared by following the procedures from Example 11, using 2-mercapto-5-chlorobenzyl alcohol to give 3.98g (60%) of 2-((4-chloro-2-(hydroxymethyl)phenyl)thio)-5-(trifluoromethyl)benzaldehyde as a light yellow oil.

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Anal. Calc. for $C_{15}H_{10}ClF_3O_2S$: C, 51.96; H, 2.91; Cl, 10.22, S, 9.25
Found: C, 51.99; H, 3.00, Cl, 10.08; S, 9.18

EXAMPLE 26

Preparation of 5-Chloro-2-((2-((methylamino)methyl)-4-(trifluoromethyl)phenyl)thio)benzyl alcohol

A mixture of 2-((4-chloro-2-(hydroxymethyl)phenyl)thio)-5-(trifluoromethyl)benzaldehyde (1.98g), toluene (100ml), 40% solution, methylamine also H_2O (2.1ml) and a catalytic amount of p-toluenesulfonic acid was heated to reflux overnight using a Dean Stark for removal of water. Solvent was evaporated to dryness to afford a light yellow oil which was dissolved in a mixture of toluene (55ml) and 95% ethanol (83ml). Sodium borohydride was added (0.55g) and the resulting suspension was stirred at room temperature overnight. Solvent was evaporated to dryness, water was added to the residue and product was extracted with EtoAc. Purification by liquid chromatography on silica gel with EtoAc/ CH_2Cl_2 (3:1) gave the free base which was dissolved in EtoAc and treated with Et_2O/HCl to afford 1.14g (52%) of 5-chloro-2-((2-((methylamino)methyl)-4-(trifluoromethyl)phenyl)thio)benzyl alcohol, as a white solid, mp. 236-237°C.

Anal. Calc. for $C_{16}H_{15}ClF_3NOS.HCl$: C, 48.25; H, 4.05; Cl, 17.80; N, 3.52; S, 8.05
Found: C, 48.25; H, 4.08; Cl, 17.75; N, 3.51; S, 8.12

EXAMPLE 27

Preparation of 5-Chloro-2-((2-((dimethylamino)methyl)-4-(trifluoromethyl)phenyl)thio)benzyl alcohol

This compound was prepared from 2-((4-chloro-2-(hydroxymethyl)phenyl)thio)-5-(trifluoromethyl)benzaldehyde by following the procedure from Groves (J.Am.Chem. Soc., 106, 630 (1984)). Purification by liquid

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chromatography on silica gel with $\text{CH}_2\text{Cl}_2/\text{EtoAc}$ 3:1 gave the free base which was dissolved in EtoAc and treated with $\text{Et}_2\text{O}/\text{HCl}$ to give 0.77g (33%) of 5-chloro-2-((2-((dimethylamino)methyl)-4-(trifluoromethyl)phenyl)thio)benzyl alcohol as a white solid. mp. 187-189°C.

Anal. Calc. for $\text{C}_{17}\text{H}_{17}\text{ClF}_3\text{NOS} \cdot \text{HCl}$: C, 49.52; H, 4.40; Cl, 17.20; N, 3.40; S, 7.78

Found: C, 49.60; H, 4.43; Cl, 17.14; N, 3.41; S, 7.67

EXAMPLE 28

Preparation of 2-((4-Chloro-2-(hydroxymethyl)phenyl)thio)-benzaldehyde

This compound was prepared by using 2-chlorobenzaldehyde and 2-mercapto-3-chlorobenzyl alcohol, following the procedure from Example 1. Purification by liquid chromatography on silica gel with hexanes/EtoAc 4:1 gave 17.28g (56%) of 2-((4-chloro-2-(hydroxymethyl)-phenyl)thio)benzaldehyde as a yellow solid. mp. 92-94°C

Anal. Calc. for $\text{C}_{14}\text{H}_{11}\text{ClO}_2\text{S}$: C, 60.32; H, 3.98; Cl, 12.72; S, 11.50
Found: C, 60.01; H, 4.07; Cl, 12.75; S, 11.52

EXAMPLE 29

Preparation of 5-Chloro-2-((2-(3-(dimethylamino)propyl)phenyl)thio)benzyl alcohol

A mixture of 2-((4-chloro-2-(hydroxymethyl)phenyl)thio)benzaldehyde (14.99g), (2-dimethylaminomethyl)triphenyl phosphonium bromide (27.81g, potassium carbonate (11.13g) formamide (2.05g) and anhydrous 1,4-dioxane (56ml) was heated at 95°C for 4hrs. Filtered and evaporated solvent to dryness. The residue was purified by liquid chromatography on silica gel with 15% MeOH/EtoAc to give a cis-trans mixture, 0.62g was dissolved in glacial acetic acid and catalytic

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hydrogenation with 10% Pd-C was carried out at 30psi. Catalyst was filtered off and solvent was evaporated to dryness. Residue was taken up in EtOAc and basified with 1N NaOH to pH 11. Purification by liquid chromatography on silica gel with 10% MeOH/roluene gave the free base which was dissolved in EtOAc and treated with $\text{Et}_2\text{O} \cdot \text{HCl}$ to afford 0.16g (23%) of 5-chloro-2-((2-(3-dimethylamino)propyl)phenyl)-thio benzyl alcohol as an off-white hygroscopic solid.

Anal. Calc. for $\text{C}_{18}\text{H}_{22}\text{ClNOS} \cdot \text{HCl}$; C, 58.06; H, 6.23; Cl, 19.94; N, 3.76; S, 8.61

Found: C, 57.97; H, 6.24; Cl, 19.12; N, 3.71, S, 8.56

EXAMPLE 30

Activity Studies

Uptake of ^3H -Biogenic Amines in Crude Synaptosomal Preparations of Rat Hypothalamus and Striatum

A 0.5 mL aliquot of a crude synaptosomal preparation prepared according to the technique of Ferris *et al.*, J. Pharm. Exp. Ther., 181, 407 (1972) and Patrick *et al.*, J. Pharm. Exp. Ther., 241, 152 (1987) was incubated in a standard incubation medium containing 10 M iproniazid, 1 M ascorbate and 0.1 M of either ^3H -dopamine, ^3H -1-norepinephrine or ^3H -serotonin. Final volumes were 3 mL.

All incubations were conducted for 3 minutes under an atmosphere of 95% O_2 -5% CO_2 . The uptake at 0°C and 37°C was determined in each experiment and the difference between the two determinations represented the accumulation of ^3H -amine by the temperature-dependent uptake process. Test compounds were dissolved in the standard incubation medium and preincubated with the crude synaptosomal preparation for 5 minutes, before the addition of the labeled substrate.

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Reactions were stopped by the addition of 2 mL of ice-cold 0.32 M sucrose containing 25 mM Tris buffer, pH 7.4, and rapid cooling in an ice-bath. Samples were centrifuged at 49,600 x g for 10 minutes.

The resulting pellet was washed with 5 mL of 0.9% saline and again centrifuged. The washed pellet was resuspended in 2 mL of 0.4 N perchloric acid and centrifuged to remove the precipitated protein. A 1 mL aliquot of the supernatant was taken for determination of radioactivity.

Table II

IC₅₀ (Molar) for inhibition of Biogenic Amine Uptake
(Values in parentheses indicate % inhibition at 10⁻⁵ M.)

Compound	Norepinephrine*	Dopamine*	Serotonin
Example 2	(59.3 ± 4.9%)	(64.0 ± 1.0%)	4.1 ± 2.3 x 10 ⁻⁸
Example 5	(55.0 ± 13.6%)	(55.0 ± 0.0%)	1.2 ± 0.2 x 10 ⁻⁷
Example 7	4.2 ± 0.5 x 10 ⁻⁷	9.3 ± 2.1 x 10 ⁻⁷	4.9 ± 0.8 x 10 ⁻⁹
Example 9	(62.5 ± 6.2%)	(61.0 ± 5.7%)	2.9 ± 1.5 x 10 ⁻⁸
Example 12	(57.3 ± 1.2%)	(48.0 ± 1.7%)	6.8 ± 1.9 x 10 ⁻⁹
Example 15	(59.0 ± 8.7%)	(63.5 ± 7.5%)	1.7 ± 0.8 x 10 ⁻⁸
Example 17	(45.0 ± 3.0%)	(42.0 ± 1.0%)	9.3 ± 0.6 x 10 ⁻⁹

*Percent inhibition is mean of triplicate assay.

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EXAMPLE 31FormulationsA. Tablet

<u>Ingredient</u>	<u>Amount per Tablet</u>
A compound of formula (I) (as the base)	150 mg
Lactose	85 mg
Cornstarch	50 mg
Micronized silica gel	10 mg
Polyvinylpyrrolidone	5 mg

The lactose, cornstarch and compound of formula (I) are mixed together and granulated with a binder (polyvinylpyrrolidone in an alcoholic solution) to form granules. The granules are passed through a 16-20 mesh screen, then air dried, lubricated with micronized silica gel and compressed into tablets. A film coat may then be applied if desired.

B. Capsule

<u>Ingredient</u>	<u>Amount per Capsule</u>
A compound of formula (I) (as the base)	150 mg
Lactose	125 mg
Cornstarch	125 mg

The above ingredients are mixed and filled into a two piece hard gelatin capsule.

C. Parenteral Solution

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<u>Ingredient</u>	<u>Amount per Ampule</u>
A compound of formula (I) (as the pharmaceutically acceptable salt)	125 mg (calculated as free base)

Sterile water for injections, q.s. to 1.0 mL

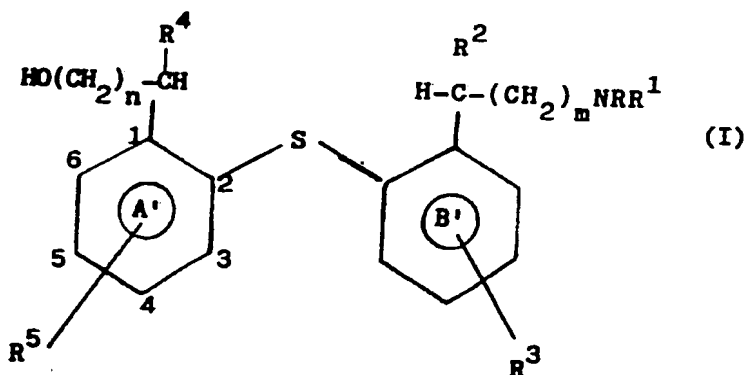
A pharmaceutically acceptable salt of a compound of formula (I) is dissolved in sterile water under sterile conditions to make 1.0 mL. Such a solution may be packaged in a sealed sterile ampoule to provide a unit dose or in a sterile vial for multiple doses. If the formulation is to be packed in a multi-dose container, the addition of a bacteriostat such as 0.2 to 0.5% w/v of phenol is desirable.

D. Suppository

150 mg of the hydrochloride salt of a compound of formula (I) is mixed with 250 mg of softened or salted cocoa butter, and a suppository is formed by chilling and shaping in a mold.

WHAT WE CLAIM IS :-

1. A compound of the formula (I)



wherein n and m are the same or different and are each 0, 1, 2 or 3;

R and R^1 are the same or different and are each hydrogen or straight or branched C_{1-6} alkyl;

R^2 and R^4 are the same or different and are each hydrogen or C_{1-4} alkyl;

R^3 and R^5 are the same or different and are each hydrogen, halo (e.g. fluoro, bromo, iodo, chloro), trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkylthio, nitro or NR^6R^7 wherein R^6 and R^7 are the same or different and are hydrogen or C_{1-3} alkyl;

provided that both R^3 and R^5 are not hydrogen and further provided that when n and m are 0, R^2 and R^4 are hydrogen and R^5 is halo and is in the 5 position of the phenyl ring (A'), then R^3 cannot be hydrogen;

or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof.

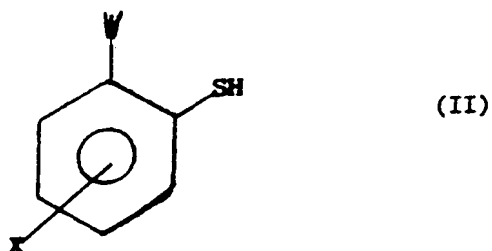
2. A compound as claimed in claim 1, wherein R and R^1 are each methyl.

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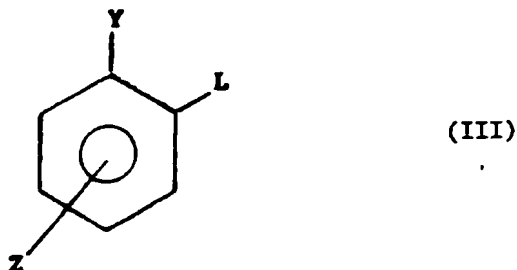
3. A compound as claimed in claim 1 wherein R^2 and R^4 are hydrogen.
4. A compound as claimed in claim 1 wherein R^3 or R^5 is chlorine.
5. A compound as claimed in claim 1 wherein R^3 or R^5 is tri-fluoro methyl.
6. A compound as claimed in claim 1 wherein when either R^3 or R^5 is tri-fluoro methyl the other is chlorine.
7. A compound according to claim 1 wherein R^4 is hydrogen and n is 0.
8. A compound according to claim 1 wherein when R^2 is hydrogen and m is 0, R and R^1 are both methyl.
9. 2-((4-chloro-2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof.
10. 2-((4-chloro-2-((dimethylamino)methyl)phenyl)thio)-5-(trifluoromethyl)benzyl alcohol or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof.
11. 2-((2-((dimethylamino)methyl)phenyl)thio)-5-(trifluoromethyl)-benzyl alcohol or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof.
12. 4-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof.
13. 3-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol or a pharmaceutically acceptable ester, salt or other

physiologically functional derivative thereof.

14. 2-chloro-6-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof.
15. 5-chloro-2-((2-((dimethylamino)methyl)phenyl)thio)- α -methylbenzyl alcohol or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof.
16. A process for the preparation of a compound as defined in any one of claims 1 to 15 or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof, which comprises reacting a compound of formula (II).



wherein X is R^3 or R^5 and W is $\text{HO}(\text{CH}_2)_n\text{CH}(\text{R}^4)$ or a precursor thereto or $\text{R}^1\text{RN}(\text{CH}_2)_m\text{CHR}^2$ or a precursor thereto and R^1 , R^2 , R^3 , R^4 , R^5 , m and n are as hereinbefore defined with a compound of formula (III)



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wherein Z is R^5 or R^3 , Y is $R^1RN(CH_2)_mCH(R^2)$ or a precursor thereto or $HO(CH_2)_nCH(R^4)$ or a precursor thereto and R^1 , R^2 , R^3 , R^4 , m and n are as hereinbefore defined and L is a suitable leaving group.

17. A pharmaceutical formulation which comprises a compound of formula (I) or pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof according to any one of claims 1 to 15 in association with a pharmaceutically acceptable carrier.
18. A compound as claimed in any of claims 1 to 10 for use in therapy.
19. Use of a compound or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof as claimed in any of claims 1 to 15 in the manufacture of a medicament for the prophylaxis or treatment of a condition selected from one of the following:-
 - depression
 - anxiety
 - obsessive compulsive disorders, and
 - alcoholism.
20. Use of a compound or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof as claimed in any of claims 1 to 15 in the manufacture of a medicament for the potentiation of the analgesic effect of morphine.
21. A method of treating a mammal suffering from a condition selected from one of the following:-

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depression

anxiety

obsessive compulsive disorders, and

alcoholism,

comprising administering to the mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof as defined in any one of claims 1 to 15.

22. A method of potentiating the analgesic effect of morphine in a mammal comprising administering to the mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof as defined in any one of claims 1 to 15.

INTERNATIONAL SEARCH REPORT

PCT/GB 92/02295

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07C323/32; A61K31/135		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07C	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 402 097 (THE WELLCOME FOUNDATION LIMITED) 12 December 1990 cited in the application see the whole document ---	1-15, 19
A	US,A,4 056 632 (N.B. MEHTA ET AL.) 1 November 1977 cited in the application see the whole document -----	1-15, 19
<p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 23 FEBRUARY 1993		Date of Mailing of this International Search Report - 2. 03. 93
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer FINK D.G.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB92/02295

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claims 21,22 are directed to a method of treatment of
(diagnostic method practised on) the human/animal body the search has been
carried out and based on the alleged effects of the compound/composition."
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

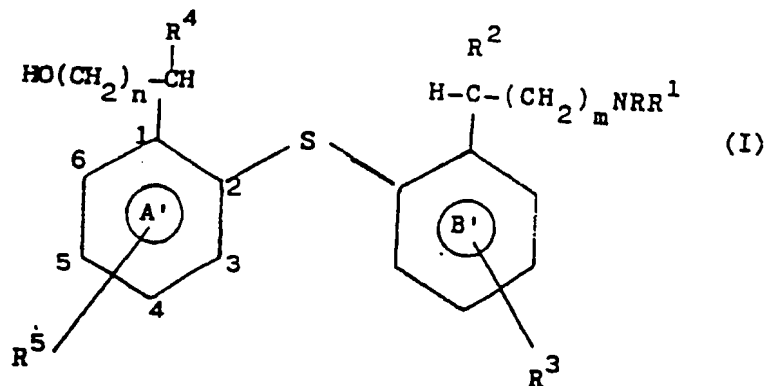
1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

A class of halogen-substituted diphenylsulfide compounds are disclosed



wherein n and m are the same or different and are each 0, 1, 2 or 3;

R and R^1 are the same or different and are each hydrogen or straight or branched C_{1-6} alkyl;

R^2 and R^4 are the same or different and are each hydrogen or C_{1-4} alkyl;

R^3 and R^5 are the same or different and are each hydrogen, halo (e.g. fluoro, bromo, iodo, chloro), trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkylthio, nitro or NR^6R^7 wherein R^6 and R^7 are the same or different and are hydrogen or C_{1-3} alkyl;

provided that both R^3 and R^5 are not hydrogen and further provided that when n and m are 0, R^2 and R^4 are hydrogen and R^5 is halo and is in the 5 position of the phenyl ring (A'), then R^3 cannot be hydrogen;

or a pharmaceutically acceptable ester, salt or other physiologically functional derivative thereof,
which produce a large selective inhibition of serotonin uptake in brain.

Such compounds are useful in the treatment or prevention of a range of depressive conditions as well as anxiety, obsessive compulsive disorders and alcoholism.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9202295
SA 67525

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 23/02/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0402097	12-12-90	AU-A- 5684190	13-12-90
		JP-A- 3024052	01-02-91
		US-A- 5095039	10-03-92
		US-A- 5104897	14-04-92

US-A-4056632	01-11-77	US-A- 3997540	14-12-76
		AT-B- 356079	10-04-80
		AT-B- 363459	10-08-81
		AT-B- 357142	25-06-80
		AU-B- 500698	31-05-79
		BE-A- 844298	19-01-77
		CA-A- 1081696	15-07-80
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		JP-B- 61013468	14-04-86
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		NL-A- 7607975	25-01-77
		SE-B- 428296	20-06-83
		SE-A- 7608203	22-01-77
		SE-A- 8007171	14-10-80
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		US-A- 4044014	23-08-77
		US-A- 4061863	06-12-77
		US-A- 4103020	25-07-78
		US-A- 4123555	31-10-78
